

# Computational Tools and Environment for Multiscale Modeling from NBCR

Wilfred W. Li, Ph.D.

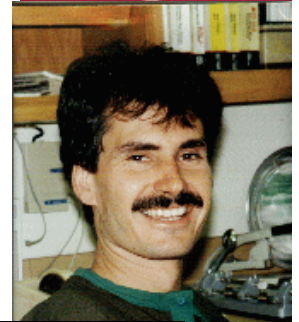
[wilfred@sdsc.edu](mailto:wilfred@sdsc.edu)

National Biomedical Computation Resource  
Center for Research in Biological Systems  
San Diego Supercomputer Center  
University of California, San Diego

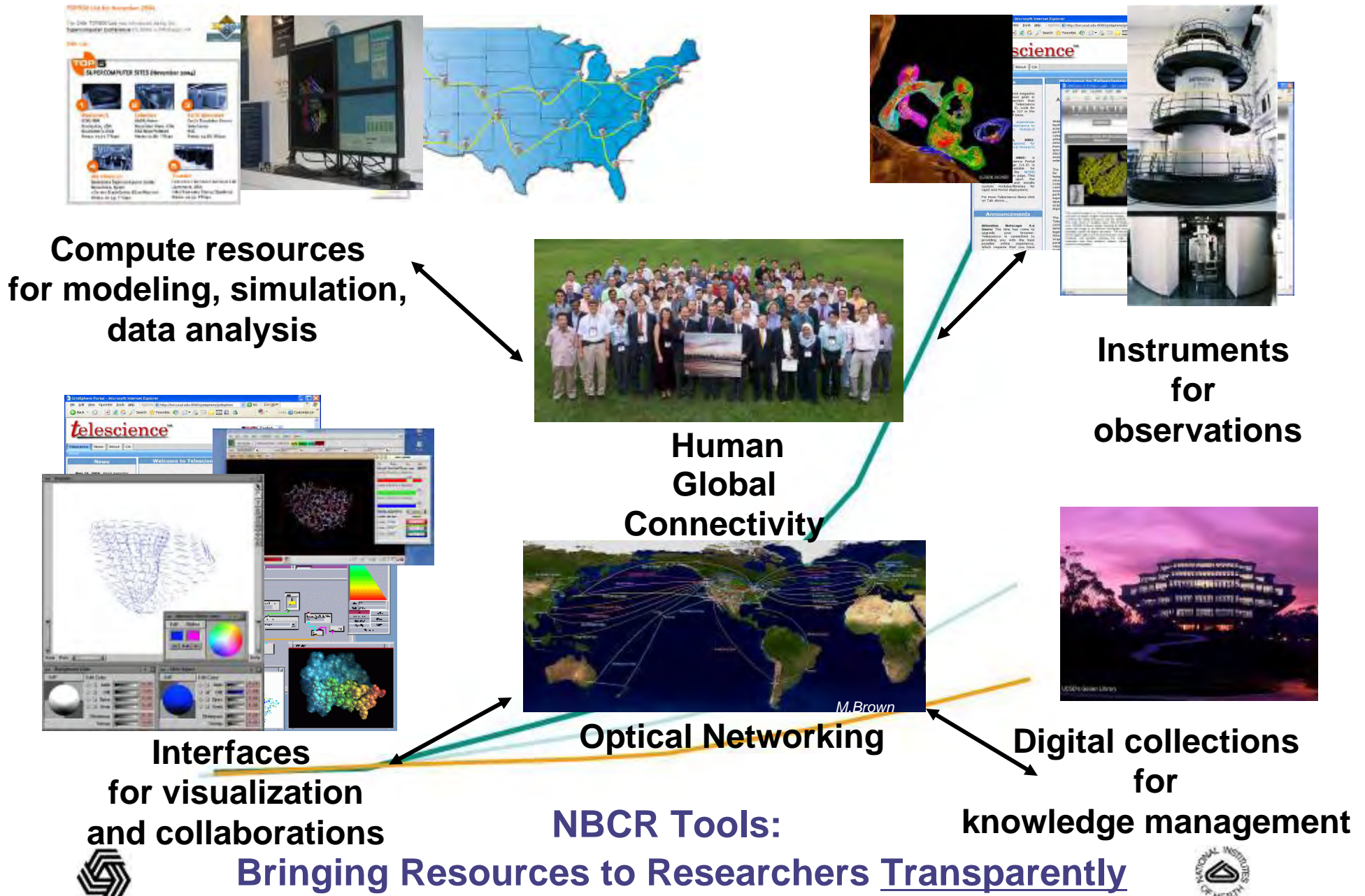


## National Biomedical Computation Resource – A National Center funded by NCRR, NIH

- J. Andrew McCammon, Chemistry
- Michael Holst, Math
- Nathan Baker, Chem/Math
- Amarnath Gupta, CS
- Kim Baldrige, Chem
- Wilfred Li, Biochem
- Andrew McCulloch, BioEng
- Anushka Michailova, BioEng
- Michel Sanner, CS
- Art Olson, Chem
- Mark Ellisman, Neurobio
- Philip Papadopoulos, EE
- Peter Arzberger, Math/Pop BIO

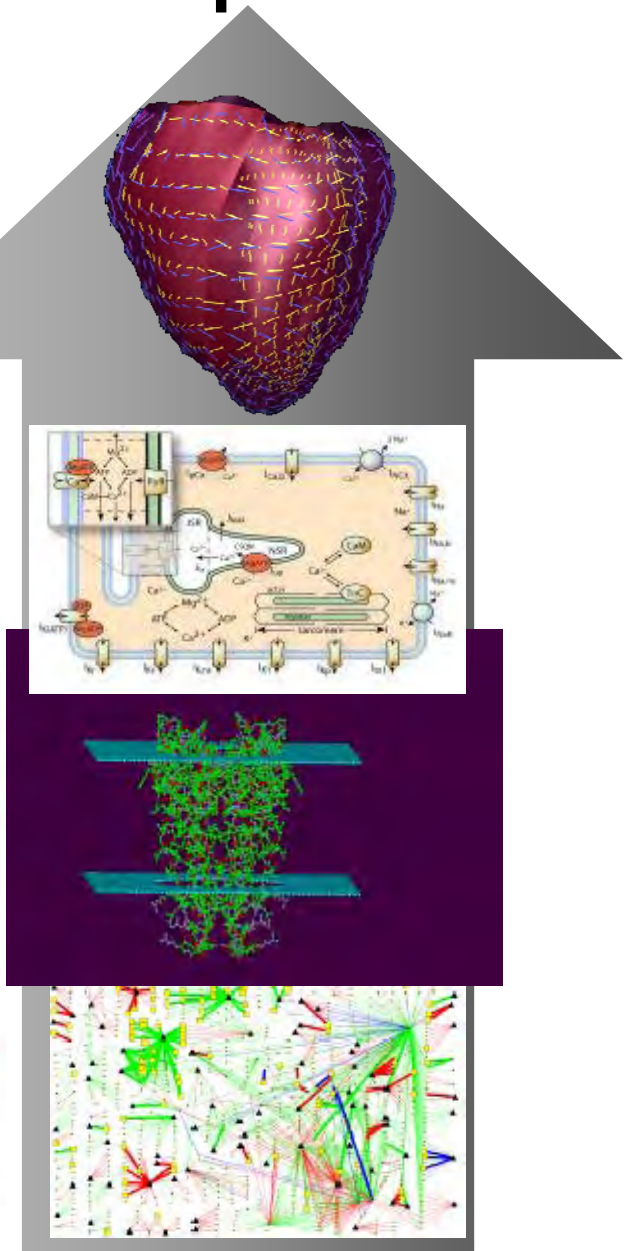
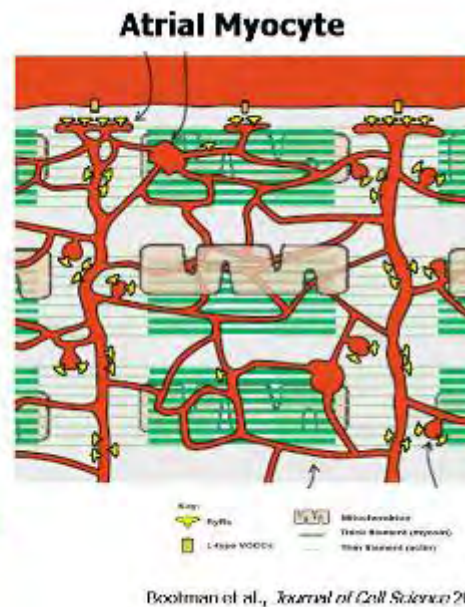
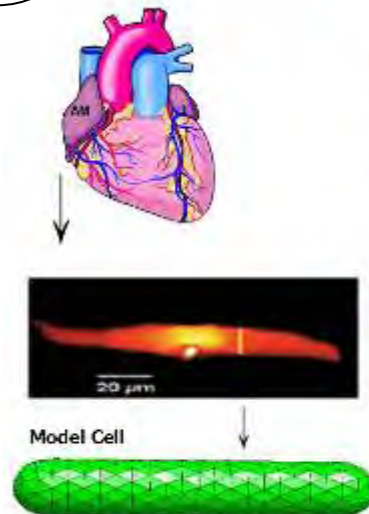
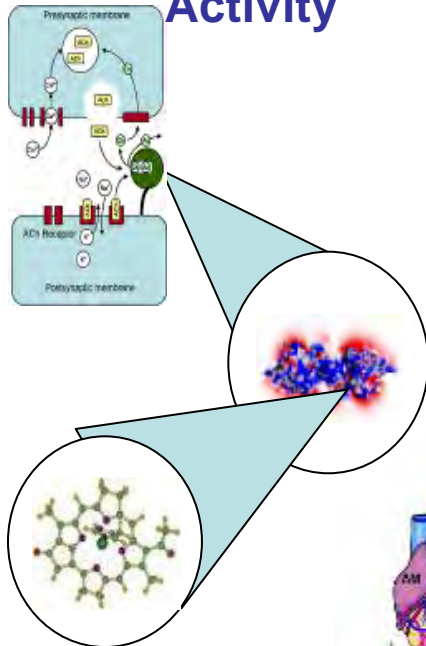


# Cyberinfrastructure: Enabling Biomedical Research



# Challenge: Biological Complexity of Multiple Scales

## Modeling Synaptic Activity

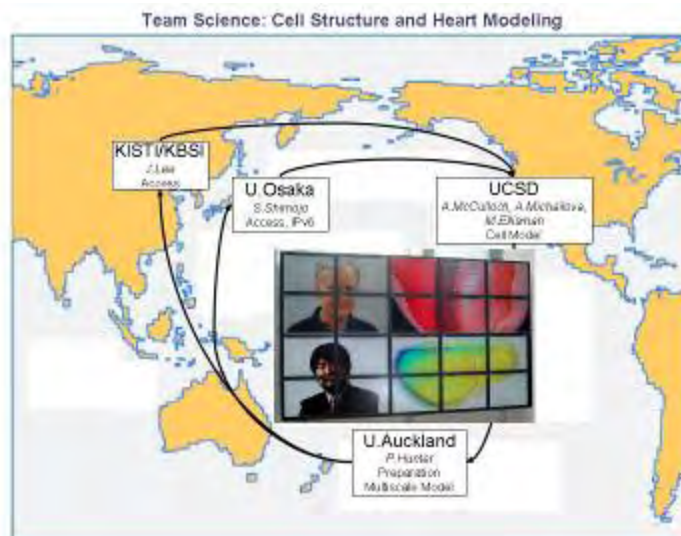


NBCR Tools: Modeling and Analysis Across Scales



# International Leverage

- Co-Develop **PRAGMA, PRIME, PRIUS**
  - Opal-OP: Opal-based service with Gt4 for PDBj, PRIUS Student, Osaka University
  - My WorkSphere, co-developed by Jilin University students, hosted by NBCR
- Open Source
  - Gfarm: Distributed File System, AIST
  - CSF4: Grid Scheduler, Jilin University
- Collaborations on Avian Flu
  - PRIME: Collaboration with CNIC, China
  - Award from TATRC (\$351K, 1 year), joint with
    - U Hawaii, AIST, Jilin, CNIC (transparent ws for data access), KISTI (portal environment for CSF4 job scheduling and query)
- Access to test bed, data, expertise: Enabling Team



# Summer Institute

## nbcrcr.net/si

CYBERINFRASTRUCTURE & MULTISCALE MODELING APPROACHES  
NATIONAL BIOMEDICAL COMPUTATION RESOURCE <http://nbcrcr.net/si/2006/>

7-11 August 2006 in La Jolla, California...

The National Biomedical Computation Resource (NBCRCR) is pleased to present its first annual Summer Institute to be held on 7-11 August 2006. This training program will provide an overview of cyberinfrastructure and multiscale modeling approaches, and include plenary sessions (day 1) and hands-on training sessions using tools essential for cutting edge biomedical research. NBCRCR's goal in offering this Summer Institute is to broaden the impact of these tools and work closely with the biomedical community in future developments, while offering significant opportunities for networking among researchers and participants.

*The specific topics to be addressed include:*

- GridSphere portals • Web services and ontology • Cluster and grid computing
- Computational cardiac electrophysiology and mechanics • Molecular visualization and virtual screening • Molecular electrostatics and diffusion

*Each of these topics represents a parallel track that will meet half days for four days. Each participant may sign up for up to two tracks.*


*Who should attend?* The workshop is geared toward graduate students, postdocs and researchers interested in learning how to use multiscale modeling tools addressed by this workshop and/or who are interested in understanding the role of cyberinfrastructure in biomedical research.

*Costs:* For individuals who do not need housing, the registration deadline is **July 1st**, and the costs are \$250 for two tracks, or \$200 for one track. For individuals who require housing and meals, the registration deadline is **July 14th**, and the cost is \$400 (4 nights), plus \$200 for each additional night.

*Scholarships:* There will be five scholarships awarded to help defray the costs of attending the meeting. Information and application forms can be found on our website. Awardees are required to present a poster during the poster sessions.

*For more information visit:* <http://nbcrcr.net/si/2006> or contact Teri Simms (619.594.1016, [tsimms@nbcrcr.ucsd.edu](mailto:tsimms@nbcrcr.ucsd.edu)). Enrollment is limited. To ensure your place in the Summer Institute program and to help us accommodate you, we ask that you register as early as possible. Please visit our website for detailed program information.

NBCRCR is a resource for the biomedical community. Our mission is to conduct, catalyze, and enable biomedical research by harnessing, developing, and deploying frontier computational, information and grid technologies. We are comprised of researchers from the University of California, San Diego, including the San Diego Supercomputer Center (SDSC), the California Institute for Telecommunications and Information Technology (Calit2), the Center for Research in Biological Systems (CRBS), The Scripps Research Institute (TSRI), and Washington University in St. Louis. NBCRCR is supported by the P41 HHS grant from the National Center for Research Resources (NCRR), National Institutes of Health (NIH). More information about NBCRCR may be found at <http://nbcrcr.net>.




- Mini Symposium
- Approx 50 participants (8 countries; 30 institutions)
- Several resources involved

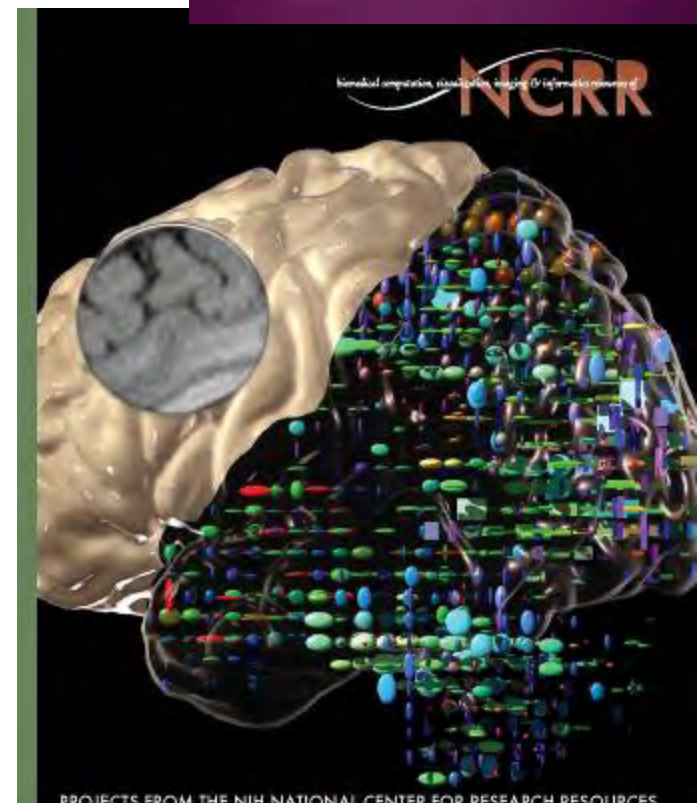


- New tutorials on line
- New users
- New/enhanced collaborations

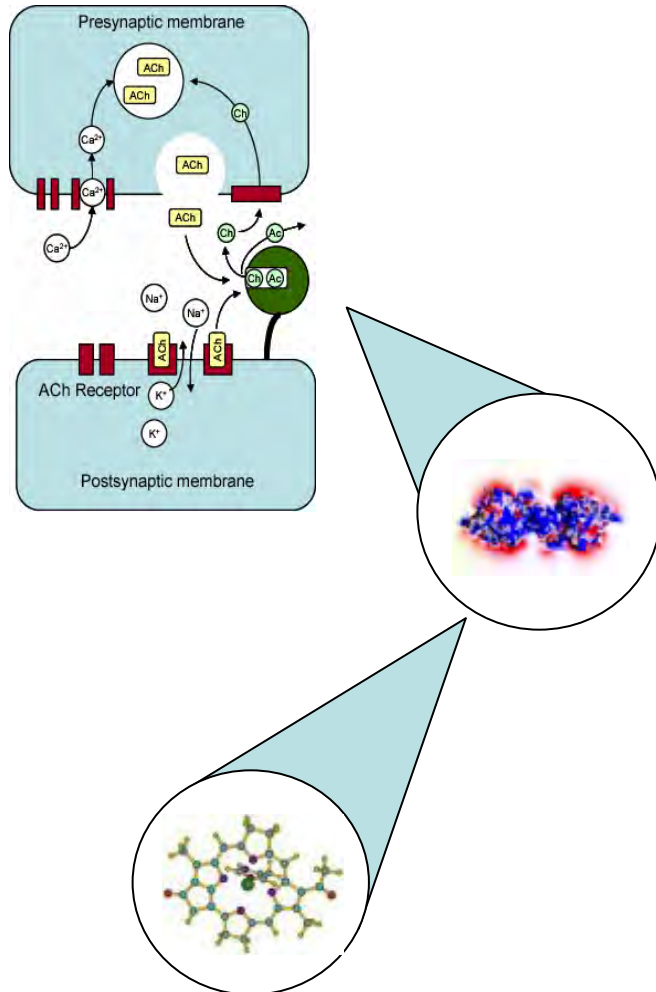


# Building Community via Interactions

- Organize Sessions
  - SC06
  - Biophysics – organized by Ferrin center
- Interact with IMAG – involved two groups (McCulloch, Li) and workshop proposal for
  - Series of workshops on Model Sharing Strategies, Software for Collaborative Research and Standards for Multiscale Biological Modeling of Tissues and Organs
- Propose multiscale modeling session – joint with SIMBIOS, at PSB, Jan 2008
- Gateway to
  - WCG:
    - Connection via Art Olson
  - OSG:
    - Frank Wuerthwein participated in Summer Institute 06
  - TeraGrid:
    - Science Gateways



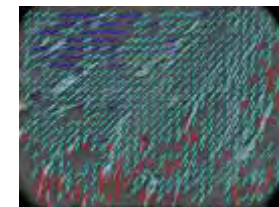
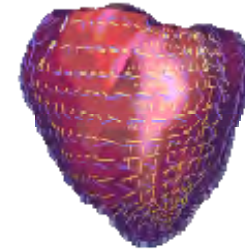
## Modeling Synaptic Activity



Neuromuscular diseases –  
Lou Gehrig's, Alzheimer's, ...

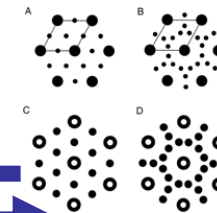


## Modeling the Heart



multicellular

ventricles



lattice



crossbridge

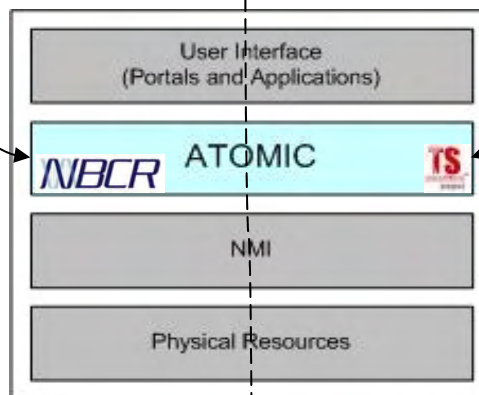


filament

Cardiovascular diseases –  
Cardiomyopathy, Arrhythmia, ...



## Transformation Based Backprojection for Volume Reconstruction (TxBR)



**TERAGRID**



# Enabling Biomedical Applications with Grid Technology -- Cyberinfrastructure

Cyberinfrastructure: raw resources, middleware and execution environment

## Virtual Organizations

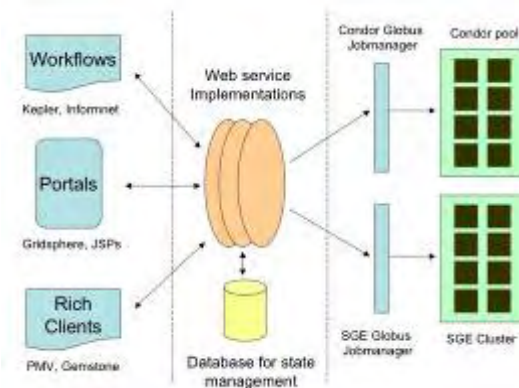
## Workflow Management

## Web Service

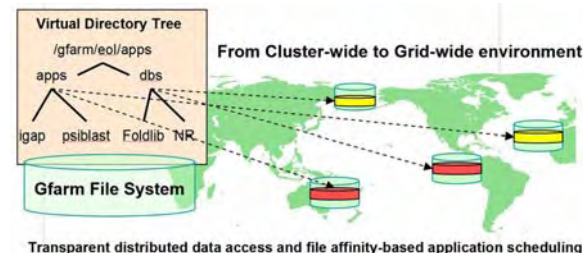
NBCR Rocks Clusters



Vision



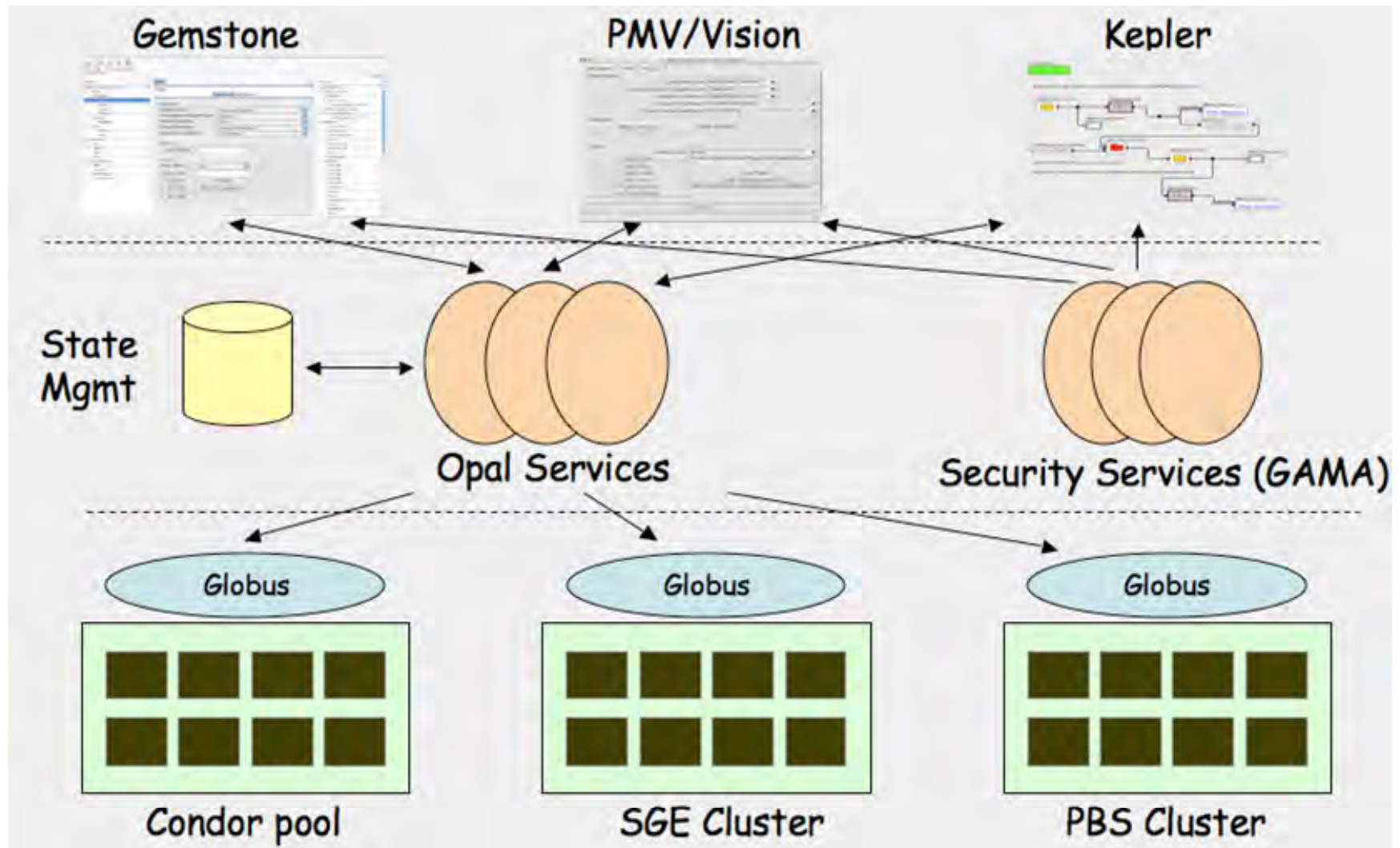
Virtual Filesystem



KEPLER



# Service Oriented Architecture

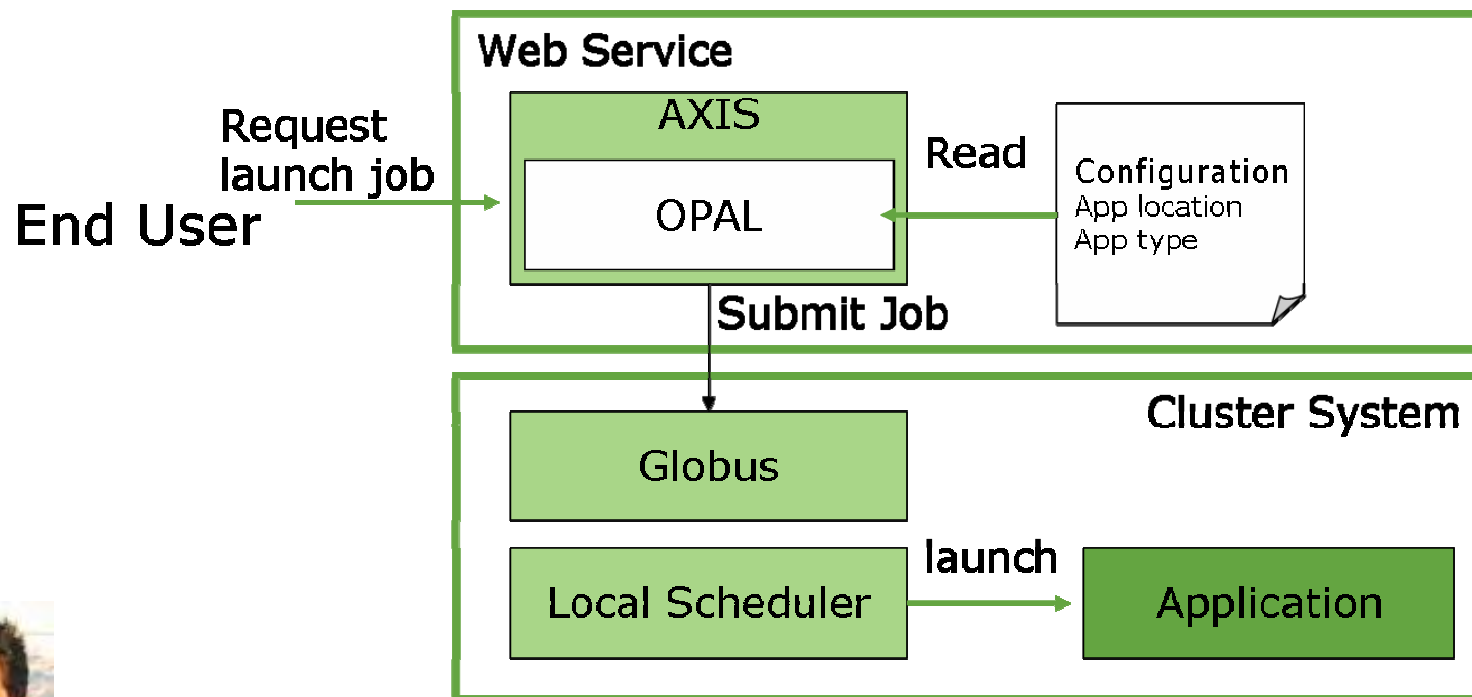


# Towards Services Oriented Architectures (SOA)

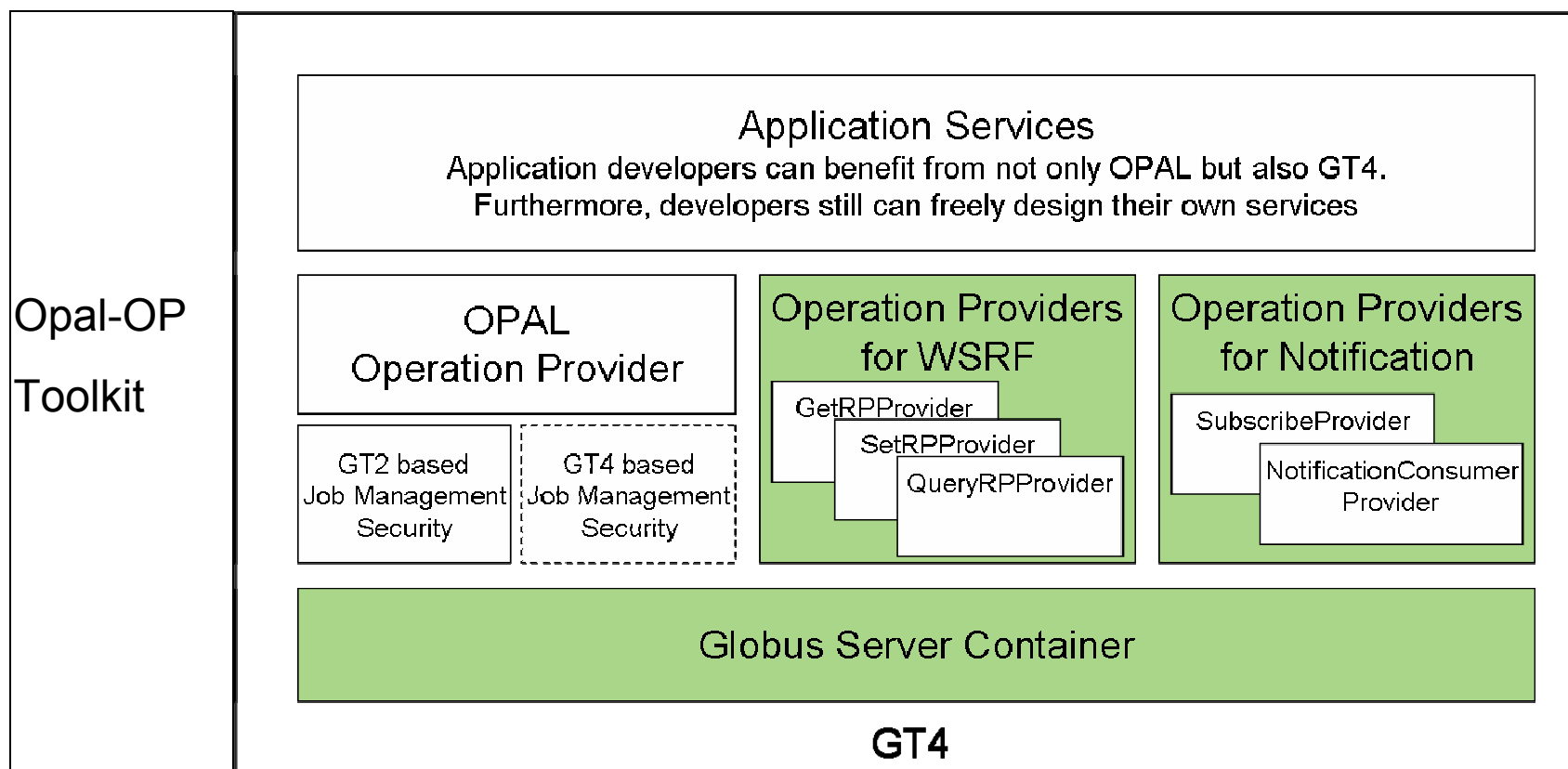
- Scientific applications wrapped as Web services
  - Provision of a SOAP API for programmatic access
- Clients interact with application Web services, instead of Grid resources
  - Used in practice in NBCR, CAMERA, GLEON, among many others
  - PDBj, BioGrid-Japan – QM/MM simulations (Opal-OP)
  - Continuity, AutoDock, APBS, PMV, GEMSTONE (Opal)



# Opal: Web Service Wrapper



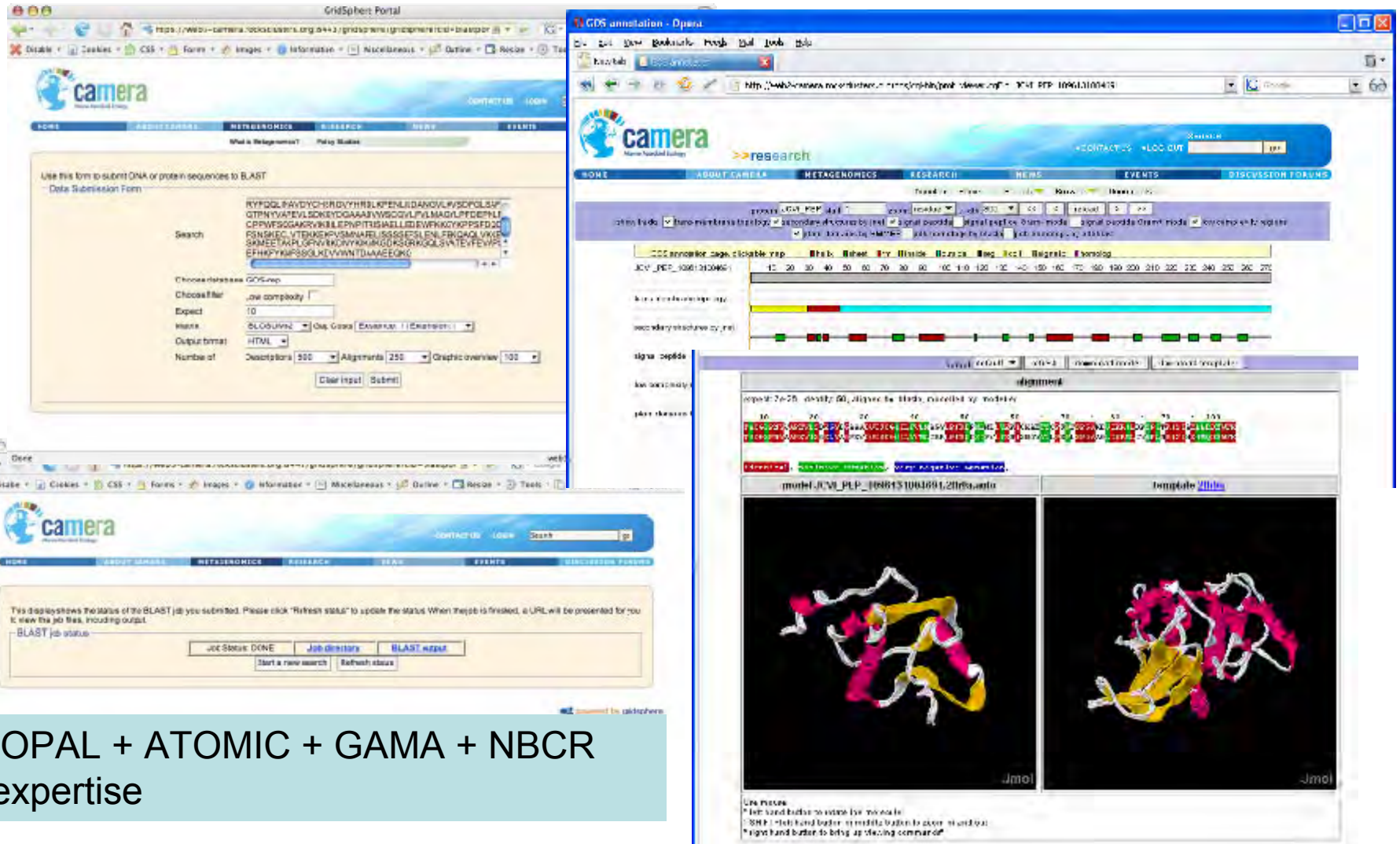
# Opal WSRF Operation Provider



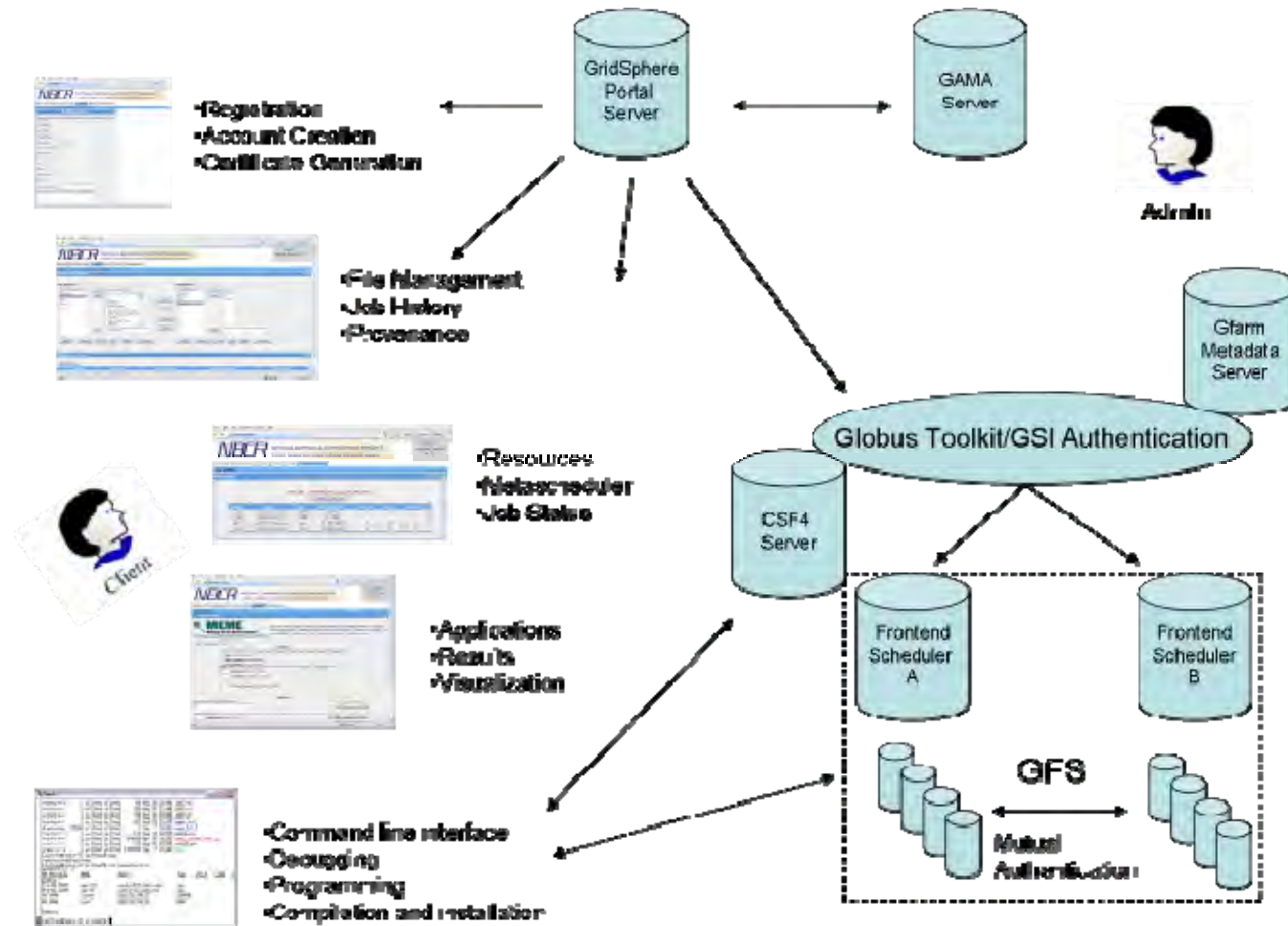
K. Ichikawa

In use at PDBj for the structure navigator

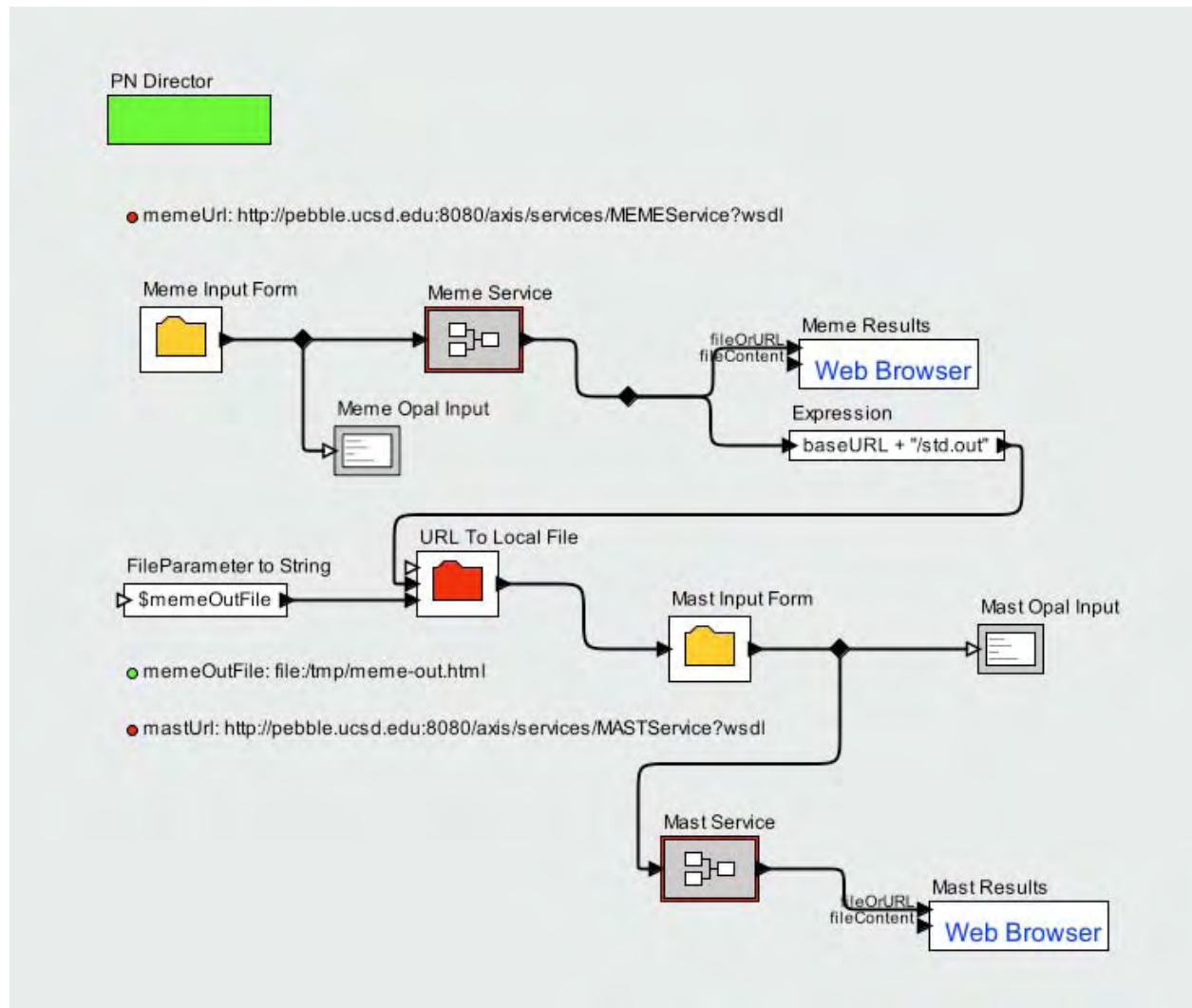




# My WorkSphere Overview



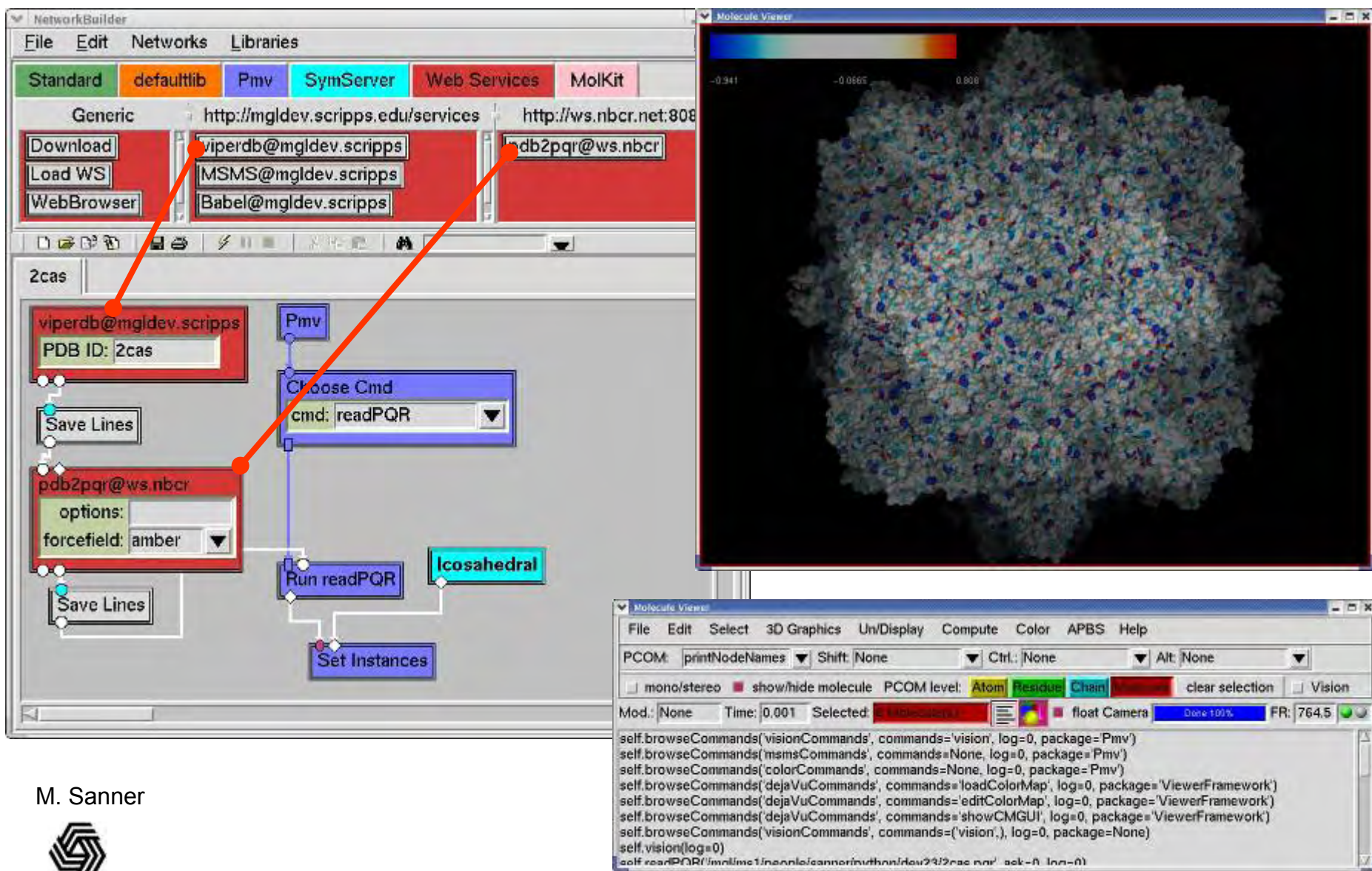
# Web Service based Workflow Composition



S. Krishnan



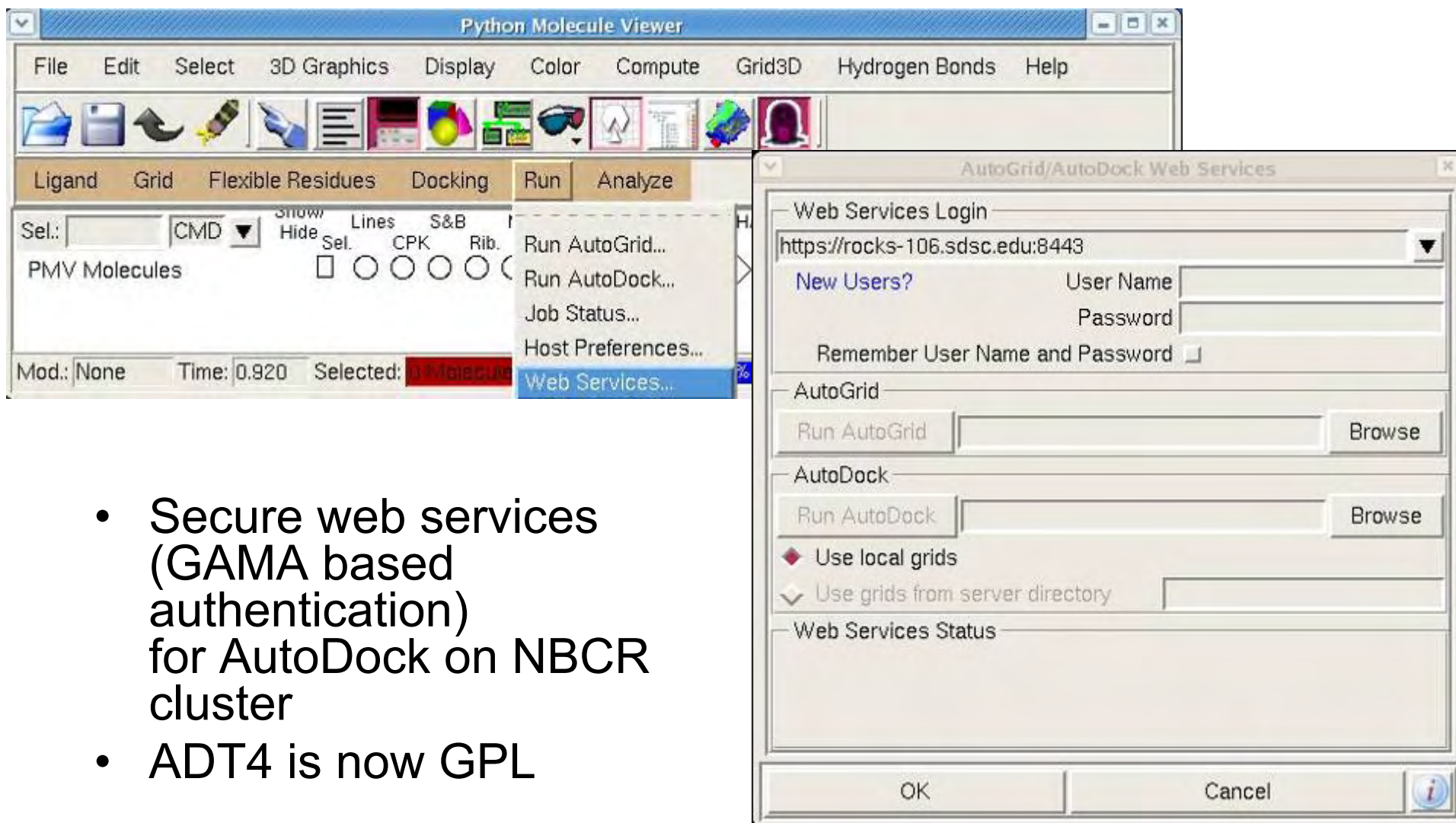
# Opal Web services in Vision



M. Sanner



# Secure AutoDock Services

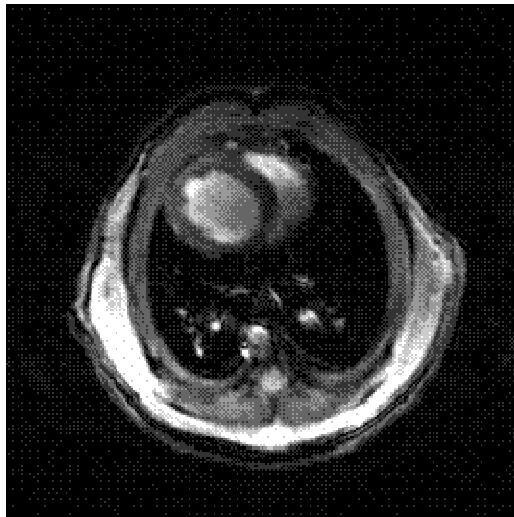


The image shows two overlapping windows from a software application. The background window is titled "Python Molecule Viewer" and has a menu bar with File, Edit, Select, 3D Graphics, Display, Color, Compute, Grid3D, Hydrogen Bonds, and Help. Below the menu is a toolbar with various icons. A sub-menu is open under the "Run" button, showing options: Run AutoGrid..., Run AutoDock..., Job Status..., Host Preferences..., and Web Services... (highlighted in blue). The foreground window is titled "AutoGrid/AutoDock Web Services" and contains a "Web Services Login" section with a URL dropdown set to "https://rocks-106.sdsc.edu:8443", fields for "User Name" and "Password", and a "Remember User Name and Password" checkbox. Below this are sections for "AutoGrid" and "AutoDock", each with a "Run" button and a "Browse" button. There are also checkboxes for "Use local grids" (checked) and "Use grids from server directory" (unchecked). At the bottom are "OK" and "Cancel" buttons.

- Secure web services (GAMA based authentication) for AutoDock on NBCR cluster
- ADT4 is now GPL

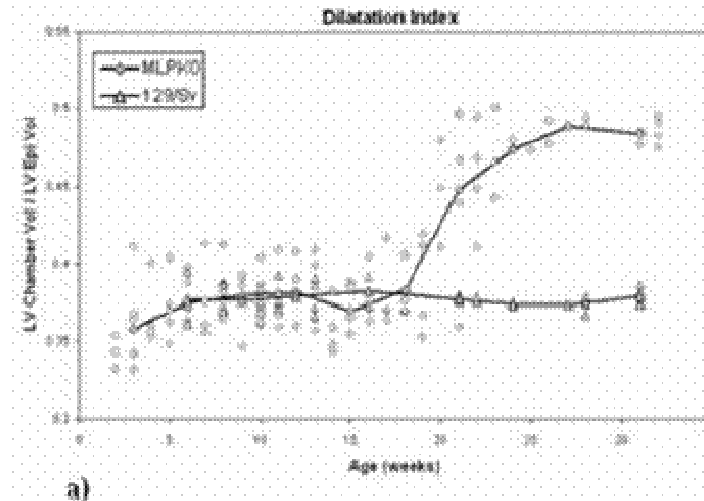


# Continuity 6.3 In Action at WHOLE HEART SCALE: MRI and Ventricular Mechanics in Murine Heart Failure

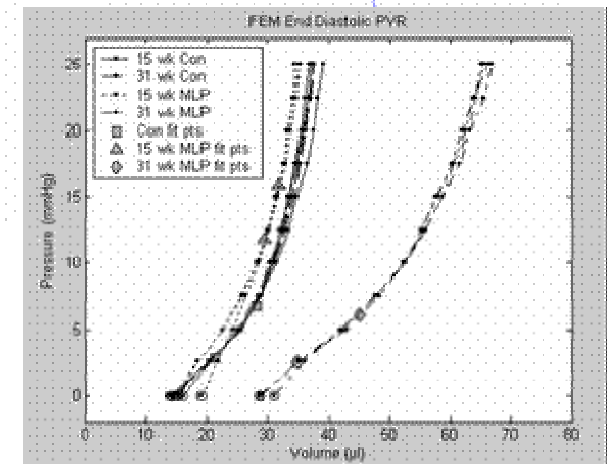
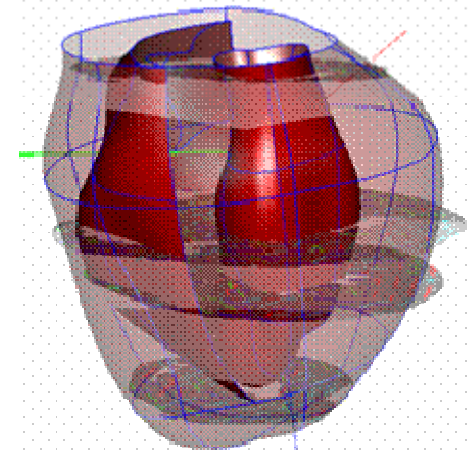


**High-field MRI**

**Costandi PN, Frank LR, McCulloch AD, Omens JH (2006) Role of diastolic properties in the transition to failure in a mouse model of cardiac dilatation. *Am J Physiol Heart Circ Physiol* 2006 Dec;291(6):H2871-8.**



**Remodeling data**

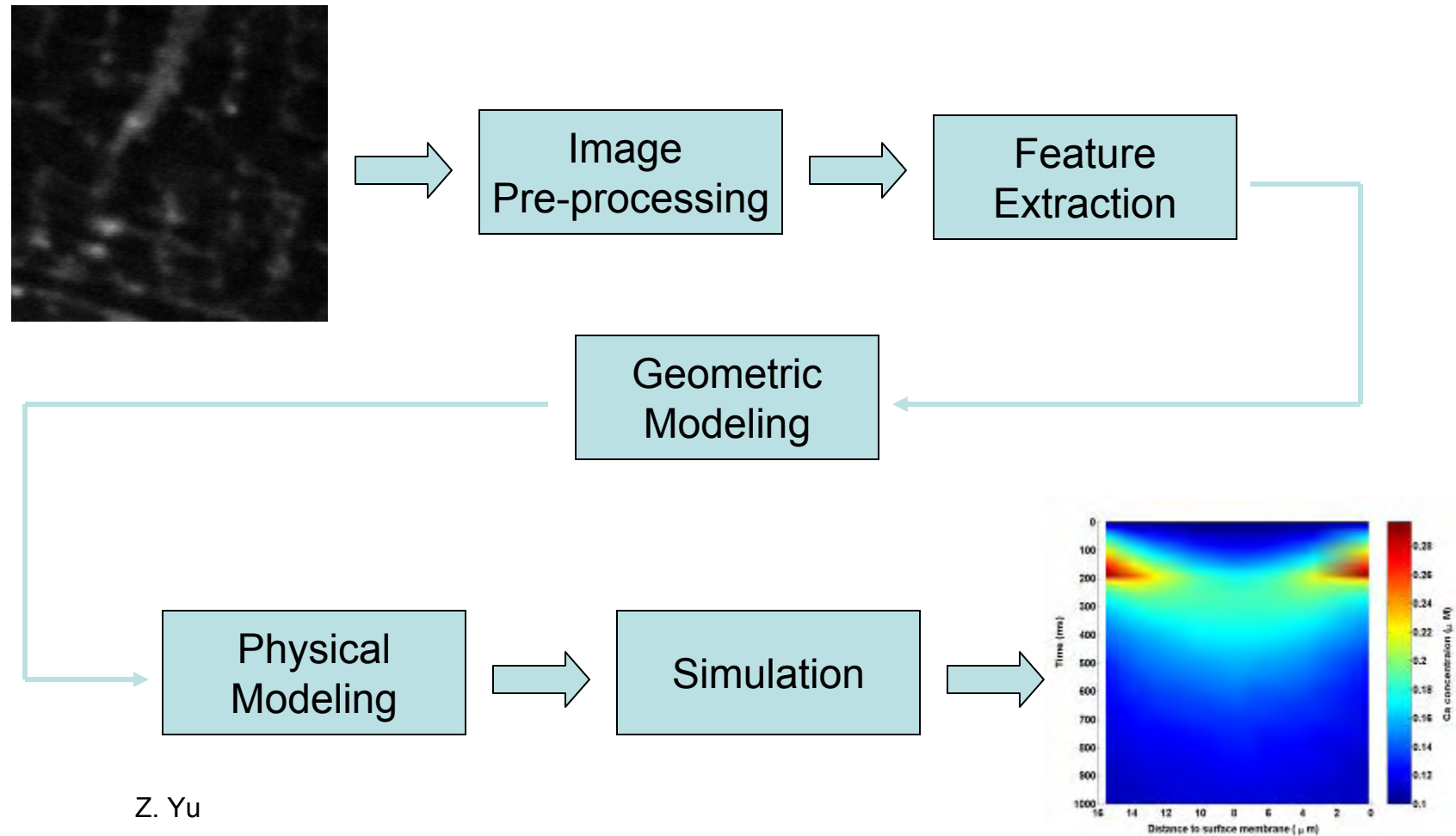


**Finite Element Model**



# Subcellular Level Modeling: Integrating Image Analysis, Mesh Generation, and Simulation

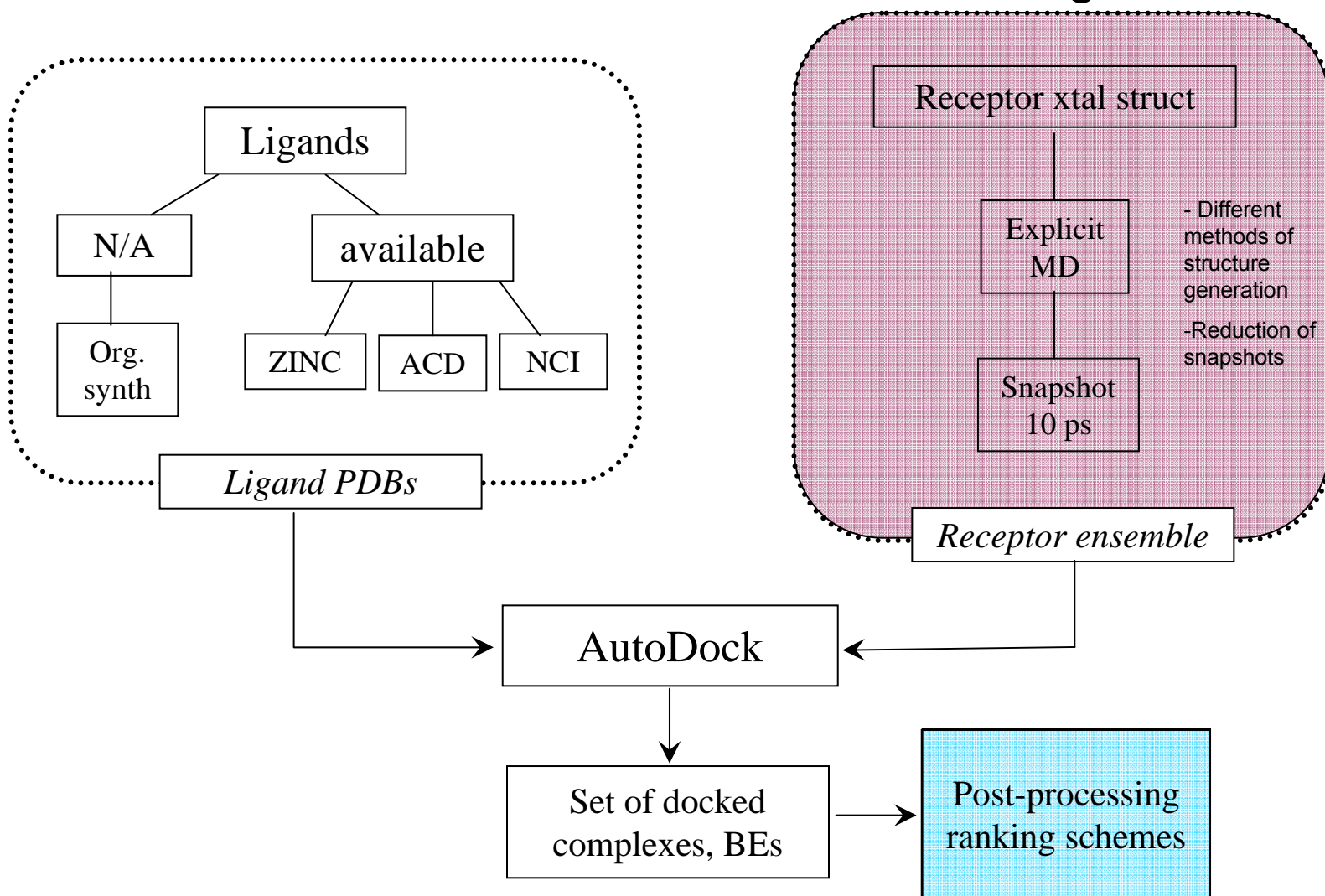
- Pipeline



Z. Yu



# Translational Medicine Research: Relaxed Complex Method and Virtual Screening



R. Amaro



# Supplementary Slides

- NBCR Web Site: <http://nbcr.net>
- Publications: <http://nbcr.net/publications.php>.
- Tools: <http://nbcr.net/tools.php>.
- Highlights: <http://nbcr.net/news.php>
- Mailing list: [announce@nbcr.net](mailto:announce@nbcr.net)
- Training & Dissemination: <http://nbcr.net/userservices.php> and <http://nbcr.net/pub/wiki>.

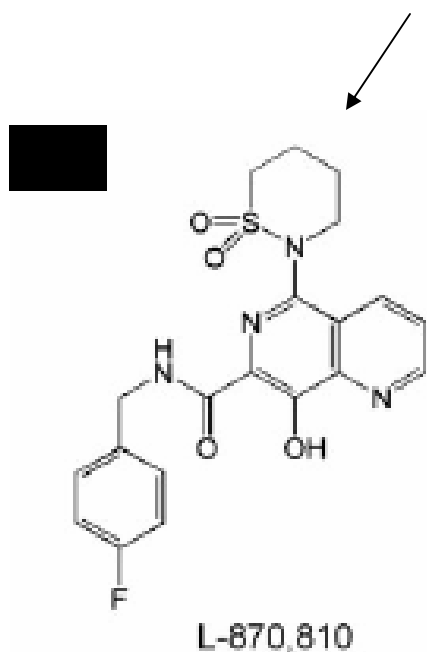


# New Class of HIV Drugs: Merck & Co.

Discovery of unexpected binding site in HIV-1 Integrase using MD and AutoDock:  
Schames, ... & McCammon, *J. Med. Chem.* (released on web, March 2004)

“ Exploration of the structural basis for this unexpected result provides insights into this class of antiviral agents and suggests an approach to the development of integrase inhibitors with unique resistance profiles.”

D. Hazuda et al., *Proc. Natl. Acad. Sci. USA* (Aug. 2004),  
refers to Schames, et al. (2004).



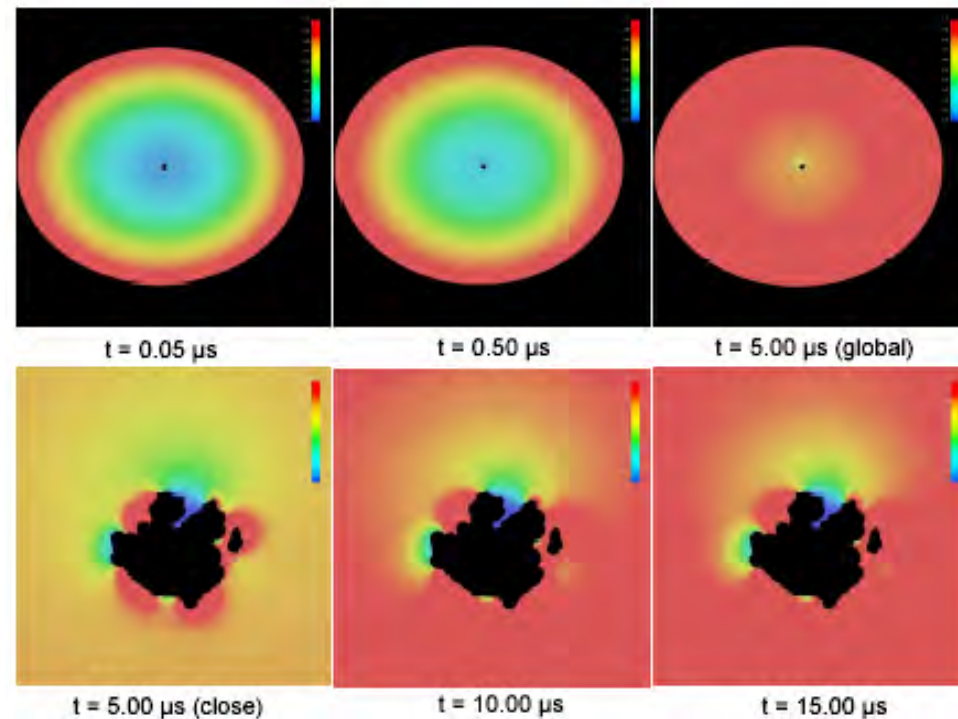
→ L-870812 →

MK-0518

February, 2006 – Phase III Clinical Trials  
<http://clinicaltrials.gov/show/NCT00293254>  
August, 2006 – Expanded Access Program



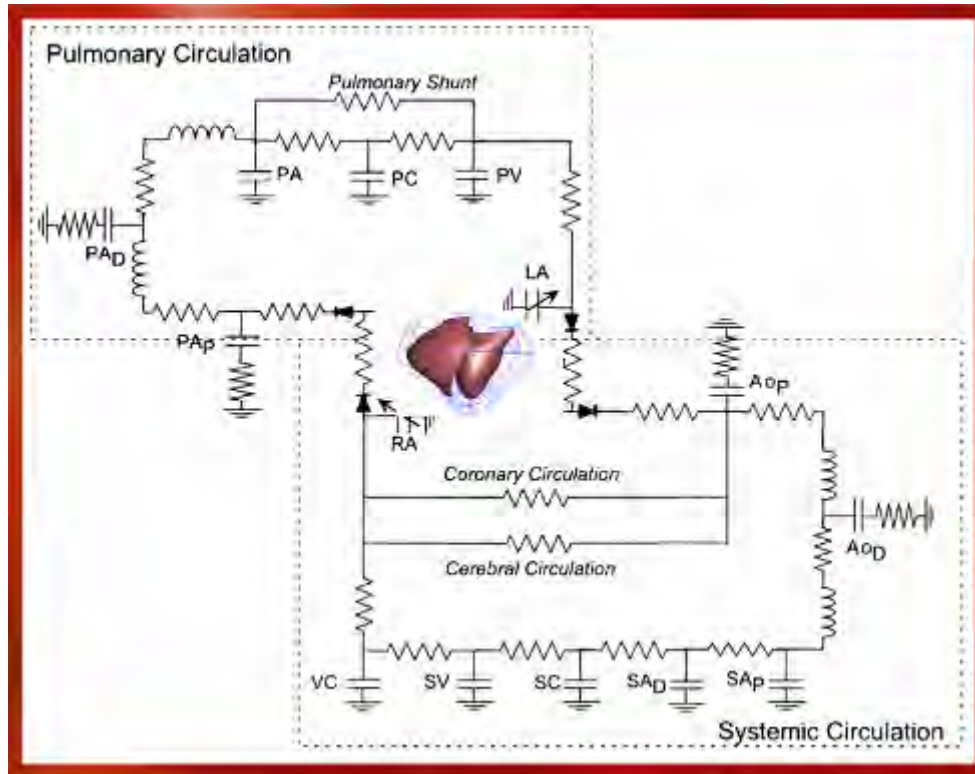
# Time-dependent Diffusional Encounter



Y. Cheng, J. Suen, D. Zhang, S. Bond, Y. Zhang, Y. Song, N. Baker, C. Bajaj, M. Holst, J.A. McCammon. Finite Element Analysis of the Time-dependent Smoluchowski Equation for Acetylcholinesterase Reaction Rate Calculations. Biophys. J. (2007).

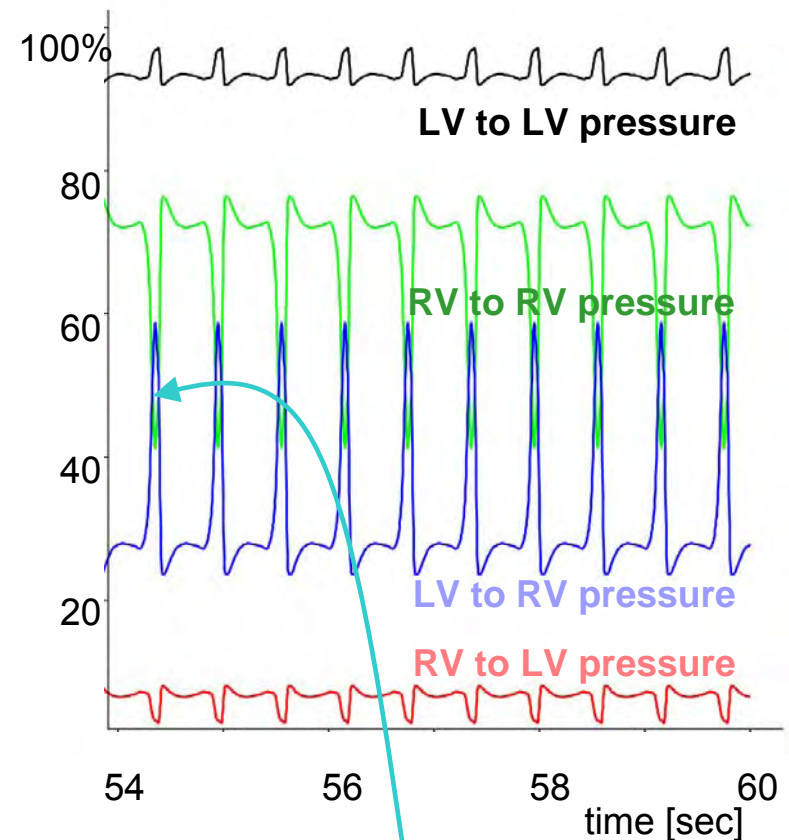


# SYSTEM SCALE: Ventricular Interactions



Integrated Multi-Scale Model

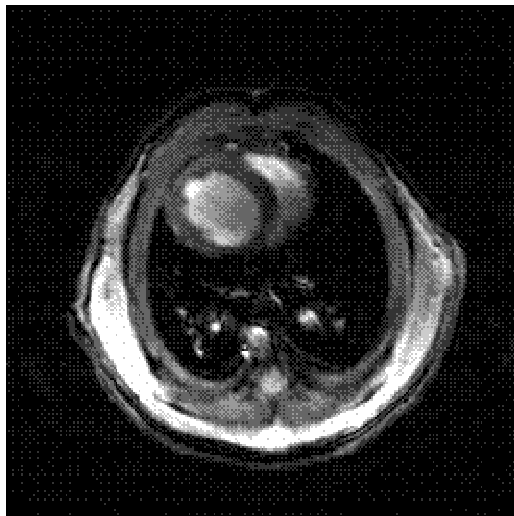
Kerckhoffs RCP, Neal M, Gu Q, Bassingthwaite JBB, Omens JH, McCulloch AD (2007) **Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonic circulation.** *Ann Biomed Eng* 35(1):1-18



In systole, the LV contributes more to RV pressure than the RV itself!

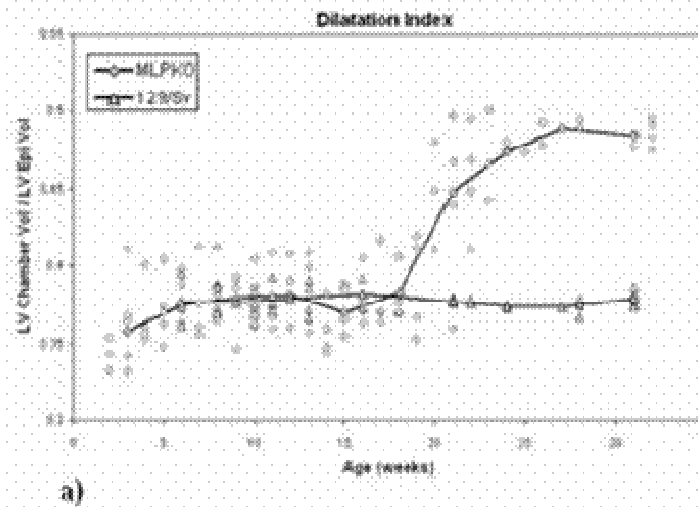


# WHOLE HEART SCALE: MRI and Ventricular Mechanics in Murine Heart Failure

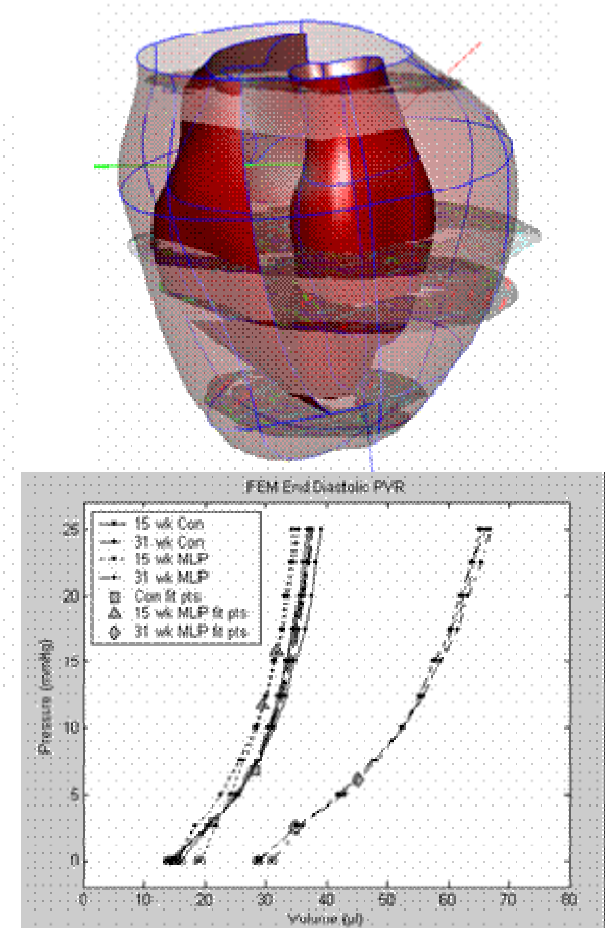


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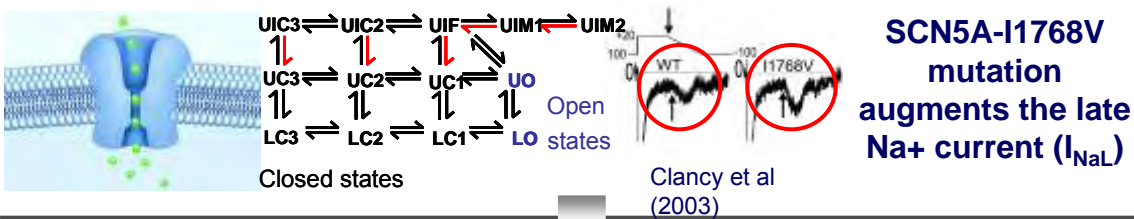


**Finite Element Model**

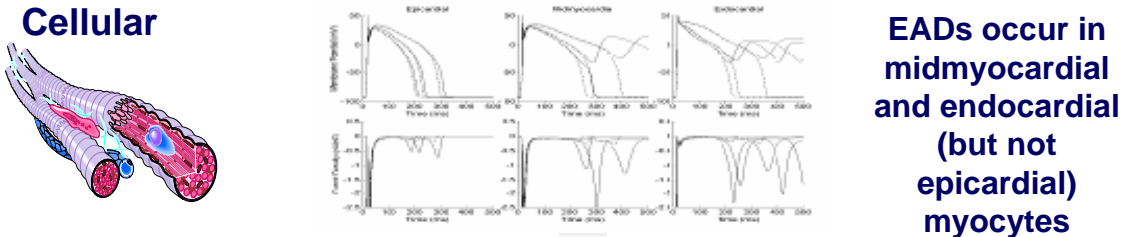


## Tissue Wedge Model of Inherited Arrhythmia in LQT3

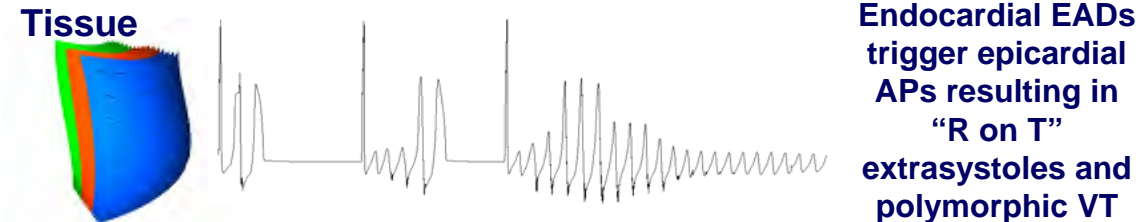
## Subcellular



## Cellular



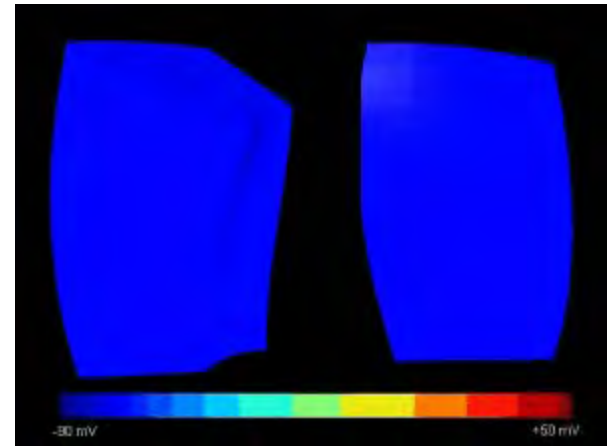
## Tissue



**SCN5A-I1768V  
mutation  
augments the late  
Na<sup>+</sup> current (I<sub>NaL</sub>)**

**EADs occur in midmyocardial and endocardial (but not epicardial) myocytes**

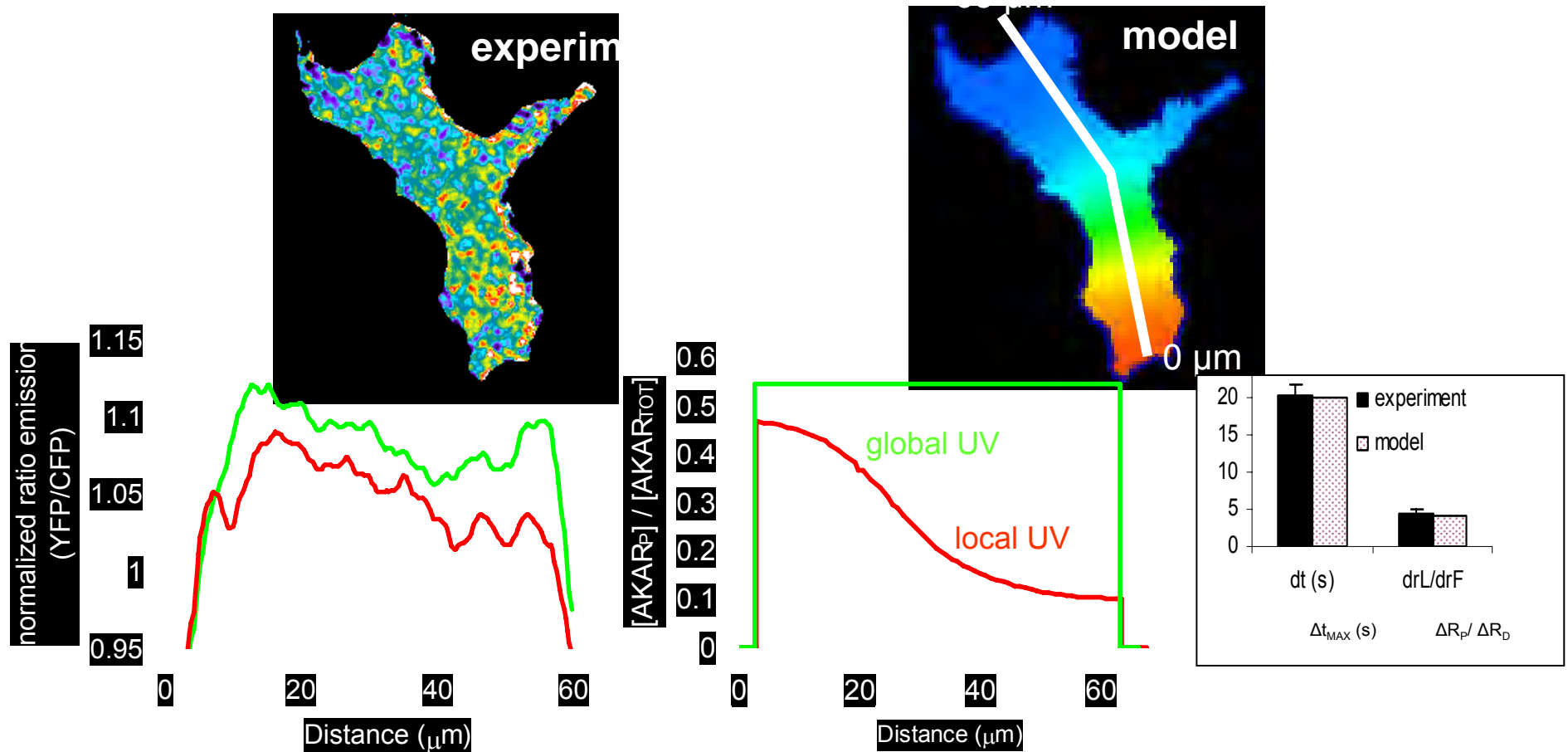
**Endocardial EADs  
trigger epicardial  
APs resulting in  
“R on T”  
extrasystoles and  
polymorphic VT**



Flaim SN, Giles WR, McCulloch AD (2006) **Contributions of sustained INa and IKv4.3 to transmural heterogeneity of early repolarization and arrhythmogenesis in canine left ventricular myocytes.** *Am J Physiol Heart Circ Physiol* 291(6):H2617-29



## SINGLE CELL SCALE: PKA-mediated phosphorylation gradients



Saucerman JJ, Zhang J, Martin JC, Peng LX, Stenbit AE, Tsien RY, McCulloch AD (2006) **Systems analysis of PKA-mediated phosphorylation gradients in live cardiac myocytes.** *Proc Nat Acad Sci* 103(34):12923-12928

